DSM-TACE of HCC: Evaluation of Tumor Response in Patients Ineligible for Other Systemic or Loco-Regional Therapies

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ZUSAMMENFASSUNG

Hintergrund Die Studie wurde durchgeführt, um das Tumoransprechen, das Überleben und die Sicherheit der Behandlung durch transarterielle Chemoembolisation mit abbaubaren Stärke-Mikropartikeln in Kombination mit Doxorubicin (DSM-TACE) bei Patienten mit inoperablen hepatzellulären Karzinomen (HCC) zu analysieren. Die Patienten wurden gemäß einer interdisziplinären Konferenz mit Kontraindikationen gegen andere lokale oder systemische Therapien eingeschlossen.

Materialien und Methoden In diese retrospektive Studie wurden 28 Patienten (23 männlich, 5 weiblich, mittleres Alter 67 Jahre) mit inoperablen HCC, Serum-Bilirubinspiegel < 3 mg/dl und Kontraindikationen gegen andere lokale oder systemische Therapien eingeschlossen. DSM-TACE wurde 3-mal alle 4–6 Wochen mit Embocept® S (15 ml) und Doxorubicin (50 mg/25 ml) durchgeführt. Die Patienten wurden zunächst mit dem Barcelona-Clinic-Liver-Cancer-System (BCLC) kategorisiert; die grundlegende Leberfunktion wurde mit dem MELD-Score evaluiert. Das Ansprechen des Tumors wurde mithilfe der modifizierten Response-Evaluation-Criteria in Solid Tumors (mRECIST) bewertet.

Ergebnisse DSM-TACE konnte bei allen 28 Patienten technisch erfolgreich durchgeführt werden. Bei der Kontrollbildgebung nach 3 Therapien lagen die Gesamtraten für das vollständige Ansprechen (CR), das partielle Ansprechen (PR), die stabile Erkrankung (SD) und die progressive Erkrankung (PD) laut mRECIST bei 14,3 %, 25 %, 39,3 % bzw. 21,4 %. In Bezug auf die BCLC-Stufen ergaben sich folgende Ergebnisse (CR, PR, PD): BCLC A (n = 8): 7,1 %, 7,1 %, 10,7 %, 1,2 %; BCLC B (n = 12): 0 %, 10,7 %, 17,9 %, 14,3 %; BCLC C (n = 5): 0 %, 3,6 %, 10,7 %, 3,6 %; BCLC D (n = 3): 3,6 %, 3,6 %, 0 %, 3,6 %. Dementsprechend zeigte die DSM-TACE ein insgesamt gutes medianes Überleben von 682 Tagen, wobei das Überleben der Patienten streng vom BCLC-Stadium abhängig war.

Schlussfolgerung DSM-TACE ist eine sichere und vielver sprechende Behandlungsalternative für Patienten mit einem inoperablen HCC, die für andere lokale und systemische Therapien nicht geeignet sind.

Kernaussagen:
- DSM-TACE ist eine sichere Behandlungsalternative für Patienten mit einem HCC, die für andere lokale und systemische Therapien nicht geeignet sind.
- DSM-TACE hatte in unserer Studienpopulation keinen Einfluss auf den MELD-Score.
- Die mit DSM-TACE behandelten Patienten zeigten ein insgesamt gutes medianes Überleben von 682 Tagen, das stark vom BCLC-Stadium abhängig war.

ABSTRACT

Purpose To analyze tumor response, survival and safety in patients with non-resectable hepatocellular carcinoma (HCC) treated with transarterial hepatic chemoembolization using degradable starch microspheres (DSM-TACE) combined with doxorubicin who had no local interventional or systemic therapy alternative according to an interdisciplinary conference.
Materials and Methods In this retrospective study, 28 patients (23 male, 5 female, median age 67 years) with unresectable HCC, serum bilirubin levels ≤3 mg/dl and contraindications to Sorafenib, RFA, SIRT or cTACE were included. DSM-TACE was performed using Embocept® S (15 ml) and doxorubicin (50 mg/25 ml) three times every 4–6 weeks. Patients were initially staged using the Barcelona Clinic Liver Cancer System (BCLC). Basic liver function was evaluated with the MELD-score. Tumor response was assessed using the modified Response Evaluation Criteria in Solid Tumors (mRECIST).

Results DSM-TACE could be technically successfully performed in all 28 patients. At control imaging after three treatments, the overall rates of complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were 14.3 %, 25 %, 39.3 % and 21.4 %, respectively, according to mRECIST. With regard to BCLC stages, the results were as follows (CR, PR, PD): BCLC A (n = 8): 7.1 %, 7.1 %, 10.7 %, 1.2 %; BCLC B (n = 12): 0 %, 10.7 %, 17.9 %, 14.3 %; BCLC C (n = 5): 0 %, 3.6 %, 10.7 %, 3.6 %; BCLC D (n = 3): 3.6 %, 3.6 %, 0 %, 3.6 %. According to this, DSM-TACE showed an overall good median survival of 682 days, although the patients’ survival was strictly dependent on BCLC stage.

Conclusion DSM-TACE is a safe and promising treatment alternative for patients with unresectable HCC who are ineligible for other loco-regional therapies.

Key Points:
- DSM-TACE is a safe treatment alternative for patients ineligible for other local or systemic treatments.
- DSM-TACE did not influence the MELD-score in our study population.
- Patients treated with DSM-TACE showed an overall good median survival of 682 days, strictly dependent on BCLC stage.

Citation Format

Introduction
Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide and has become increasingly important in the Western world, as its incidence has risen significantly over the past few decades because of improved surveillance of patients with chronic liver disease and advances in liver imaging [1, 2].

Early-stage HCC is treated with curative therapies such as liver transplantation, hepatic resection and radiofrequency ablation (RFA) according to the Barcelona Clinic Liver Cancer (BCLC) staging system [3]. For the treatment of intermediate stage HCC, palliative therapies, including transarterial chemoembolization with lipiodol (cTACE) and selective internal radiation therapy (SIRT), are frequently used. Systemic treatment with multikinase inhibitors is approved for the treatment of advanced-stage HCC.

Sorafenib, a Raf-, vascular endothelial growth factor (VEGF) receptor-, platelet-derived growth factor (PDGF) receptor-blocking multikinase tyrosine inhibitor, was the only approved agent for systemic therapy during the study period (between December 2014 and March 2016). Sorafenib significantly prolongs time to progression without significant differences concerning median time to symptomatic progression, as demonstrated by the SHARP Investigators Study Group and the Asia Pacific trial [4, 5]. Moreover, the SHARP Investigators Study Group reported that the overall occurrence of treatment-related adverse events was as high as 80 % in the Sorafenib group consisting predominantly of gastrointestinal, constitutional, or dermatologic symptoms leading to permanent treatment discontinuation in 11 % of all cases [4]. Though the recent approval of other multikinase inhibitors (Regorafenib, Lenvatinib, Cabozantinib) has significantly improved systemic treatment options for advanced HCC, limitations of significant drug toxicity and relatively short median survival times during systemic therapy remain [6].

Therefore, in our setting, BCLC A-D patients ineligible for cTACE and SIRT or systemic treatment because of side effects are highly interested in alternative loco-regional treatment options. An effective and safe alternative treatment for these patients is thus highly warranted. Previous studies on degradable starch microspheres have demonstrated that non-targeted temporary (30–40 minutes half-life) tissue embolization causes minimal to no harm and that intratumoral accumulation of co-administered chemotherapeutics is increased significantly to improve treatment efficacy [1]. Thus, the clinical development of transarterial chemoembolization with degradable starch microspheres (DSM-TACE) in combination with doxorubicin could provide a safe and effective approach for HCC therapy.

The purpose of this study was to evaluate the feasibility and safety of DSM-TACE as a lobar treatment alternative in patients with early to advanced-stage HCC who are ineligible for surgical treatment, RFA, cTACE, and SIRT, or who have rejected systemic therapy because of unbearable side effects. As a secondary endpoint, the treatment response for the evaluation of effectiveness was investigated.

Materials and Methods

Study population/design
In this retrospective single-center study, we analyzed the clinical reports of 28 patients who received three sessions of repeated DSM-TACE as recommended by the manufacturer with treatment intervals between four and six weeks apart. The study was approved by the ethics committee of our hospital. Written informed consent was waived by the institutional Review Board due to the retrospective character of the study and anonymized
data evaluation. The patient population consisted of 23 male and 5 female patients with a median age of 67 years (range: 49–85).

All patients’ treatments were evaluated by a multidisciplinary consensus at the weekly tumor board comprised of all medical specialists involved in the HCC patients’ management (hepatologist, oncologist, hepatic and transplant surgeon, nuclear physician, radiotherapist, and interventional radiologist).

The requirement for inclusion was early to advanced BCLC staged HCC in patients ineligible for surgery, RFA and cTACE, SIRT, and without indication for or ineligible for systemic therapy with Sorafenib (the only approved agent at the study period between December 2014 and March 2016). The exclusion criteria were: (a) performance status (ECOG) > 2; (b) platelet count <50 000/µL and/or international normalized ratio > 1.5; (c) severe renal impairment or serum creatinine levels ≥ 2 mg/dl; (d) doxorubicin administration contraindications; and (e) bilirubin levels > 3 mg/dl. We included one patient with Gilbert’s syndrome, who initially showed an elevated bilirubin level of 4.6 mg/dl. Vascular invasion as well as (non-)neoplastic portal vein thrombosis were not considered exclusion criteria. In our setting contraindications for cTACE were: lesion count > 3, lesion size > 7 cm, decompensated cirrhosis, progress under cTACE therapy, and missing hypervascularization in DSA (digital subtraction angiography). Contraindications for SIRT were poor baseline liver function (total bilirubin levels > 2 mg/dl), exaggerated and uncorrectable hepatopulmonary shunting or reflux into arteries supplying the gastroduodenal region. Baseline characteristics of the study population are stated in Table 1.

Embolic Agent and Embolization Procedure

DSM-TACE was performed in an angiography suite with monitoring of vital signs by an interventional radiologist with at least seven years of experience in interventional procedures. Under local anesthesia, the right common femoral artery was punctured. Using the Seldinger technique, a 5F sheath was placed to secure the access site. Selective hepatic angiography was then performed with a diagnostic catheter. The tip of the catheter was placed in the celiac trunk, common hepatic artery or proper hepatic artery. Diagnostic hepatic angiography was then performed to show the anatomy of the hepatic arteries and any possible anatomical variations. Shunts to the gastrointestinal tract were identified. For selective lobar cannulation, a microcatheter was coaxially placed in the right or left hepatic artery that was feeding the affected lobe, excluding any branching shunts to extrahepatic organs such as the gastrointestinal tract to limit extrahepatic injection of the treatment.

Under fluoroscopic guidance, a suspension of 450 mg/7.5 ml of DSM (EmboCept® S, PharmaCept, Berlin, Germany) was mixed with 50 mg/25 ml of doxorubicin and 17.5 ml of contrast agent (Ultravist 300, Bayer Vital, Germany) as recommended by the manufacturer. It was slowly and continuously administered at the lobar level until blood flow sub-stasis was observed (“leaf-less tree”) or a maximum dose of 75 mg of doxorubicin was reached. For cases in which more than 450 mg of DSM was needed to achieve sub-stasis, a second suspension was prepared with 25 mg of doxorubicin, 225 mg/3.75 ml of DSM, and 8.75 ml of contrast agent. If stasis could not be reached, we injected a few ml of lipiodol (Lipiodol Ultra-Fluid, Guerbet, France) until sub-stasis was reached at a lobar level (only in cases with no portal vein thrombosis). After embolization, (temporary) vascular occlusion was confirmed with an additional angiography examination of the hepatic artery. Technically successful procedures were defined first by the reaching of a catheter position in which the
entire involved part of the liver could be treated and, second, by the ability to either infuse the full maximal dose of doxorubicin (75 mg) or reduce the flow substantially by visual control.

As premedication, all patients received 2.5 mg Metamizole and 3 mg Granisetron perinterventionally to prevent possible side effects such as pain and nausea, respectively.

**Patient safety and response evaluation**

Therapy-related side effects were evaluated by analyzing, first, the occurrence of complications according to the CIRSE Classification System for Complications documented in the angiography report and, second, the final doctor’s report at the time of hospitalization. As treatment follow-up, the overall disease control (ODC) was used, calculated as the sum of patients with complete response (CR), partial response (PR), and stable diseases (SD) using the modified Response Evaluation Criteria in Solid Tumor (mRECIST) [7, 8]. According to the manufacturer, therapy response should be evaluated after three therapy sessions at the earliest. Based on this, the therapy response in this study was assessed consistently after three therapy sessions only. In patients who received more than three DSM treatments, for example because of good response, only survival, complications and laboratory values were recorded in all subsequent interventions. Based on mRECIST, local tumor progression (TP) was defined as treatment failure. A multiphase CT exam was performed between one and three days prior to every treatment procedure and at least every four to six weeks thereafter [9, 10].

**Blood values**

The blood values of the patient before and six weeks after each TACE procedure were assessed retrospectively. The following values were recorded: AFP, GPT, albumin, bilirubin, platelets, and creatinine. Subsequently, the MELD score was calculated with the formula for patients older than 12 years with a creatinine < 4.0:

\[
\text{MELD} = (0.957 \times \ln(Cr) + 0.378 \times \ln(bilirubin) + 1.120 \times \ln(INR) + 0.643) \times 10.
\]

For the follow-up evaluation, the blood values for each TACE procedure were divided by the baseline blood value to visualize deviations from baseline.

**Statistical analysis**

Kaplan Meier survival curves were created using Prism 7 (GraphPad Software, USA). An unpaired t-test was used to compare variables such as bilirubin levels before and after DSM-TACE using Prism 7 (GraphPad Software, USA). Statistics were expressed as mean and standard deviation (SD). P-values of < 0.05 were considered significant.

**Results**

**Patient characteristics**

Between December 2014 and March 2016, 28 patients (23 male, 5 female, median age: 67 years) not eligible for SIRT or cTACE with BCLC stage A to D were enrolled. HCC was proven in all patients either by histological diagnosis or imaging criteria, according to the American Association for Study of Liver Disease (AASLD) [9].

The main clinical features of the patients and tumors are reported in Table 1. Three of the patients had undergone previous hemi- or partial resection of the right liver lobe, and one patient had undergone radiofrequency ablation of a single HCC lesion in the right lobe. Moreover, one patient had an HCC recurrence in a transplanted liver.

Before starting the treatments, three patients showed extrahepatic metastases, two in abdominal lymph nodes, one in the lung. In three patients, vessel invasion with partial portal vein thrombosis was diagnosed.

Nine patients were considered ineligible for SIRT because of deteriorated liver function (total bilirubin higher than 2 mg/dl). The others were ineligible because of pulmonary or intestinal shunts.

**Treatment feasibility and tolerance**

A total of 134 treatments were performed in 28 patients. Technically successful procedures were achieved in all patients. In particular, in all treatments, it was possible to deliver either the maximum planned dose of 75 mg of doxorubicin or to reduce the flow visually (Fig. 1).

Complications, according to CIRSE guidelines, are shown in Fig. 2. The length of hospital stay was 3.6 days on average and ranged from 2 to 10 days. MELD scores were stable with 9.08 at baseline and 8.63 after three treatment sessions.

**Tumor response**

After three treatment sessions, six patients showed progressive disease (PD 21.4 %, 6/28), four patients complete response (CR 14.3 %, 4/28), seven patients partial response (PR 25 %, 7/28, Fig. 2) and 11 patients stable disease (SD 39.3 %, 11/28) with an overall disease control rate (ODC) of 78.6 %. Progressive disease was seen in five patients after the second therapy and in one patient after the third treatment procedure. The overall survival rate after six months was 100 %. Table 3 shows the heterogeneity of the patient population regarding Child-Pugh scores and BCLC stages. The AFP value increased from 5998 to 14 748 after three treatment sessions (Fig. 3). However, the AFP value did not correlate with the therapy response. All in all, the AFP values showed a high standard deviation of 24 455 at baseline and 56 420 after three DSM-TACE procedures.

**Survival**

Although the patients’ survival (Fig. 4, Table 4) was strictly dependent on BCLC stage, patients treated with at least three DSM-TACE procedures (range = 3–9; mean = 3.8; SD = 1.8) showed an overall good median survival of 682 days. In the follow-up, 21 of 28 patients died, 7 patients were censored at the date of the last known visit or therapy. The median survival of patients with BCLC stage A HCC was not calculable (N/A) due to the high rate of censored patients (5/8) resulting from the high survival rate of BCLC A patients. However, the mean time to the last visit (5/8) or death (3/8) of BCLC A patients was 1185 days.
Blood values

All blood values (Fig. 3) indicating liver and kidney function were relatively stable over up to 9 DSM-TACE procedures. The AFP values showed, on average, a slow increase but did not correlate with therapy response after three DSM-TACE sessions. The MELD scores of the patients were stable over up to 9 TACE procedures. Out of 1134 blood values collected, a total of 36 (3%) were

Table 2

Complications that occurred during or after 134 DSM-TACE interventions according to CIRSE guidelines.

<table>
<thead>
<tr>
<th>complication</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIRSE 1°</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>CIRSE 2°</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>CIRSE 3°</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>CIRSE 4°–6°</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3

Tumor response rates regarding Child-Pugh scores and BCLC stages.

<table>
<thead>
<tr>
<th></th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>SD (%)</th>
<th>PD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>child-pugh</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A (n = 19)</td>
<td>17.9</td>
<td>32.1</td>
<td>14.3</td>
<td>3.6</td>
</tr>
<tr>
<td>B (n = 6)</td>
<td>3.6</td>
<td>3.6</td>
<td>7.1</td>
<td>7.1</td>
</tr>
<tr>
<td>C (n = 3)</td>
<td>3.6</td>
<td>3.6</td>
<td>0</td>
<td>3.6</td>
</tr>
<tr>
<td>sum:</td>
<td>25.1</td>
<td>39.3</td>
<td>21.4</td>
<td>14.3</td>
</tr>
<tr>
<td>BCLC stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A (n = 8)</td>
<td>7.1</td>
<td>7.1</td>
<td>10.7</td>
<td>3.6</td>
</tr>
<tr>
<td>B (n = 12)</td>
<td>0</td>
<td>10.7</td>
<td>17.9</td>
<td>14.3</td>
</tr>
<tr>
<td>C (n = 5)</td>
<td>0</td>
<td>3.6</td>
<td>10.7</td>
<td>3.6</td>
</tr>
<tr>
<td>D (n = 3)</td>
<td>3.6</td>
<td>3.6</td>
<td>0</td>
<td>3.6</td>
</tr>
<tr>
<td>sum:</td>
<td>10.7</td>
<td>25</td>
<td>39.3</td>
<td>25.1</td>
</tr>
</tbody>
</table>

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease.
missing (4/162 INR; 0/162 creatinine; 0/162 platelets; 0/162 GPT; 18/162 AFP; 14/162 albumin; 0/162 bilirubin).

**Discussion**

In this patient setting, DSM-TACE was safe and effective, achieving an ODC of 78.6% after three therapy procedures. In addition to that, after DSM an overall good median survival rate of 682 days in patients with progress under therapy or contraindications to SIRT, surgery, RFA, sorafenib, or cTACE was observable. No post-procedure sequelae were found, even though the study group was a high-risk population for standard local regional therapy options. In particular, three patients had thrombosis of the right portal vein, three showed extrahepatic metastases initially, three were Child-Pugh C class, five were BCLC C stage, and nine of them had deteriorated liver function with a bilirubin level between 2–3 mg/ dl. Supporting our results, Iezzi et al. showed that the usage of DSM-TACE in six patients with advanced HCC...
(only BCLC stage C) leads to an ODC of 66.6 % [11]. Furthermore, Orlacchio et al. showed that DSM-TACE combined with doxorubicin could be used as a safest treatment option to downstage HCC in six of seven patients to meet Milan criteria so that they could profit from liver transplantation [12].

Additionally, the transient blood flow obstruction generated by DSM-TACE allowed treatment repetition in all patients three times in a time interval of four to six weeks with a reduced risk of liver toxicity that may occur when using repeated conventional TACE [3, 13, 14].

Finally, DSM-TACE was not offset by any postprocedure sequelae or relevant deterioration of liver function. Quite the contrary: using DSM-TACE lead to slightly decreasing MELD scores. Other studies have also reported no postprocedure sequelae of using DSM-TACE with doxorubicin [11, 12]. Other potential alternative treatment options in patients with bilirubin levels higher than 2 mg/dl include the off-label use of SIRT or the use of drug-eluting beads. The role of SIRT in these patients is currently still under investigation and, to the best of our knowledge, there is no published data on its use in that indication. The safety and feasibility of drug-eluting beads as a further treatment alternative was reported in several previous studies [15, 16]. To our knowledge, there is no study comparing drug-eluting beads with degradable starch microspheres. Both DSM-TACE and drug-eluting beads loaded with doxorubicin may be used in HCC patients with serum bilirubin levels higher than 2 mg/dl.

On the other hand, there is not much evidence for treatment alternatives for patients that are ineligible for SIRT or TACE except for systemic therapy with Sorafenib or more recently approved agents. Therefore, systemic therapy is considered the standard treatment option approved for patients with HCC staged as BCLC C or for those patients with a tumor progressing after loco-regional interventional therapies like SIRT or ctACE with mild to moderate impairment of the liver. However, Sorafenib (the only approved agent in the study period between December 2014 and March 2016) has a rather moderate impact on survival. Moreover, treatment-related adverse events reported in several patients lead to permanent treatment discontinuation in about 11 % of cases, and patients with severe comorbidities are considered ineligible for Sorafenib treatment [4, 5, 9, 17, 18]. The recent approval of other multikinase inhibitors, namely Regorafenib, Lenvatinib, and Cabozantinib, has significantly expanded the repertoire of systemic HCC therapy [6]. Nevertheless, these agents are burdened with overall comparable safety issues like Sorafenib and result in unsatisfying survival benefits in many patients. Therefore, other local treatment alternatives such as DSM-TACE are still required for patients with advanced HCC or when patients are ineligible for systemic therapy treatment. For this reason, we decided to retrospectively analyze all BCLC staged A to D HCC patients receiving DSM-TACE when no other local or regional therapy option was possible. TACE with DSM is believed to improve the therapeutic effect and decrease the risk of systemic side effects by only temporarily occluding the smaller arterial vessels, thus reducing the immediate washout of the chemotherapy [19].

Future randomized prospective comparative studies performed on a larger population are needed to define adequate patient selection criteria and long-term results of these therapeutic techniques. The main limitations of our study are the retrospective study design and the relatively small number of patients enrolled. However, this paper is of a technical nature, mainly aimed at defining the potential role and safety of DSM-TACE in this patient setting.

**Conclusion**

DSM-TACE appears to be a safe, well-tolerated, and effective treatment option for early to advanced HCC patients ineligible for other accepted standard local interventional treatment options like RFA, SIRT, or conventional TACE as well as for systemic treatment with Sorafenib. In contrast to DEB-TACE and ctTACE, DSM-TACE can be used safely at a lobar level without significant risk of liver damage. Further investigations with larger patient populations and longer follow-ups are warranted.

**CLINICAL RELEVANCE**

- DSM-TACE is a safe therapy alternative for patients with contraindications to other local or systemic therapies.
- DSM-TACE showed an overall good treatment response in patients with an unresectable HCC.

**Conflict of Interest**

Prof. Dr. Jens M. Theysohn has given paid lectures for the company Pharmaceut in the last 3 years. The authors declare that they have no further conflict of interest.

**References**


